AMENDMENTS TO THE DRAWINGS

Please replace Replacement Figures 1-5 (Sheets 1-5), filed August 4, 2008, with the Replacement Figures submitted herewith.

Attachment: Replacement Sheets 1-5

REMARKS

This Amendment, filed in reply to the Office Action dated November 17, 2008, is believed to be fully responsive to each point of objection and rejection raised therein. Accordingly, favorable reconsideration on the merits is respectfully requested.

Claims 8-11 are rejected. Claim 11 is objected to. Claims 8, 9 and 11 are amended herewith. Support for the amendment to Claim 8 can be found throughout the specification as originally filed, and at, for example, Table 1. Support for the amendment to Claim 9 can be found throughout the specification as originally filed, and at, for example, page 3, 2nd paragraph. Support for the amendment to Claim 11 can be found throughout the specification as originally filed, and at, for example, the paragraph bridging pages 6 and 7. Claim 10 is canceled herewith without prejudice or disclaimer. New Claim 12 is introduced, support for which can be found throughout the specification as originally filed, and at, for example, page 1, 1st paragraph and page 3, 2nd paragraph.

No new matter is added by way of this amendment. Entry and consideration of this amendment are respectfully requested.

Information Disclosure Statements

Applicants thank the Examiner for returning signed and initialed copies of the PTO Forms SB/08 that accompanied the Information Disclosure Statements filed April 4, 2005, and May 26, 2005, indicating consideration of the references therein.

Drawings

On page 2 of the Office Action, the Examiner objects to Figures 1-5, submitted April 7, 2008, and August 4, 2008, as being illegible. Further, the Examiner objects to Figure 5 as allegedly containing nucleotide and amino acid sequences not identified by unique sequence identifiers.

Whilst not agreeing with the merits of the objection, in the interest of compacting prosecution, Applicants attach herewith revised copies of Figures 1-5, of greater clarity, thus overcoming this aspect of the objection.

Regarding the aspect of the objection pertaining to the recitation of nucleotide and amino acid sequences in Figure 5, Applicants submit herewith a revised Sequence Listing incorporating the sequences recited in Figure 5. In addition, the revised Figure 5 attached herewith specifically identifies the nucleotide and amino acid sequences by SEQ ID NO. Applicants respectfully submit that such overcomes the objection.

Withdrawal of the objection is respectfully requested.

Withdrawn Rejections

1. Applicants thank the Examiner for withdrawal of the rejection of Claims 1-7 under 35 U.S.C. § 112, second paragraph.

2. Applicants thank the Examiner for withdrawal of the rejection of Claims 1-7 under 35 U.S.C. § 112, first paragraph.

Objections to the Specification

1. On page 3 of the Office Action, the Examiner objects to the specification, alleging that Table 2 is illegible.

Whilst not agreeing with the merits of the objection, in the interest of compacting prosecution, Applicants attach herewith a revised copy of Table 2. Applicants respectfully submit that such overcomes the objection.

2. On page 3 of the Office Action, the Examiner asserts that the specification fails to comply with the requirements of 37 C.F.R. §1.821-1.825, as containing nucleotide and amino acid sequences not identified by SEQ ID NO.

In response, Applicants submit herewith a revised copy of Table 2, designating the sequences recited therein with sequence identifiers. Specifically, Applicants respectfully point out that the various sequences recited in Table 2 refer to alternate codons, encoding the same or conservative amino acids, which may be used to produce an antibody with similar specificity to the 2G9 antibody. Consistent with M.P.E.P. §2422.03, which provides that "with respect to 'conservatively modified variants thereof' of a [nucleotide or amino acid] sequence, the sequences may be described as SEQ ID NO: X and "conservatively modified variants thereof," Applicants herewith amend Table 2 to indicate that the sequences recited therein pertain to "SEQ ID NOs: 4 and 5, and conservatively modified variants thereof." Applicants respectfully submit that the amendments overcome the objection.

In addition, Applicants note that the copy of Table 1 submitted with the Amendment filed April 7, 2008, contained unique sequence identifiers, and thus complied with the requirements of 37 C.F.R. §1.821-1.825.

Withdrawal of the objection is respectfully requested.

Objections to the Claims

On page 5 of the Office Action, the Examiner objects to Claim 11 under 37 C.F.R. § 1.75(c), as allegedly being of improper dependent form.

Solely to advance prosecution, and without acquiescing to the merits of the objection, applicants herewith amend Claim 8 to recite that the claimed antibody comprises a heavy-chain variable region encoded by a polynucleotide comprising the nucleotide sequence of SEQ ID NO: 1, and a light-chain variable region encoded by a polynucleotide comprising the nucleotide sequence of SEQ ID NO: 2, but is not limited to that produced by the hybridoma deposited under Accession No. FERM BP-8378. Claim 11, which is amended herewith to improve clarity, further limits the antibody of Claim 8, and thus properly depends from Claim 8.

Withdrawal of the objection is respectfully requested.

Claims 8, 9 and 11 are Definite Under 35 U.S.C. § 112, Second Paragraph

On page 4 of the Office Action, the Examiner rejects Claims 8-11 under 35 U.S.C. §112, second paragraph, as being indefinite.

Initially, Applicants note that Claim 10 is canceled herewith, without prejudice or disclaimer, mooting the rejection of this claim.

1. In one aspect of the rejection, the Examiner asserts that Claim 8 recites a monoclonal antibody "specifically recognizing HIV-infected cells and *including* apoptosis." The Examiner appears to consider such a phrase to be unclear, and suggests that the claim be amended to recite that the monoclonal antibody is capable of "inducing apoptosis of said cells upon binding" to the infected cells.

Solely to advance prosecution, Applicants herewith amend Claim 8 to recite that the claimed antibody is that which "induces" apoptosis upon cell binding. Support for such an amendment can be found throughout the specification as filed, and at, for example, page 3, 2nd paragraph. Applicants respectfully submit that the amendment overcomes the rejection.

2. In a second aspect of the rejection, the Examiner contends that recitation of "cell strain with an accession No. FERM BP-8378" in Claims 8 and 11 is confusing.

Applicants note that Claims 8 and 11 as amended do not recite such a phrase, and thus this aspect of the rejection is moot. One of ordinary skill in the art would readily ascertain the bounds of Claims 8 and 11 as amended, and thus these claims are not indefinite.

Withdrawal of the indefiniteness rejection is respectfully requested.

Claim 9 is Enabled Under 35 U.S.C. § 112, First Paragraph

On page 7 of the Office Action, the Examiner rejects Claims 9 and 10 under 35 U.S.C. § 112, first paragraph, as lacking enablement.

Specifically, the Examiner interprets Claims 9 and 10 to be directed to pharmaceutical compositions comprising an IgM monoclonal antibody capable of inducing apoptosis of HIV-infected cells, and for use in the treatment or prevention of HIV infection and the onset of AIDS. The Examiner asserts that the specification is not enabling for such subject matter, alleging that the specification fails to provide adequate guidance pertaining to the immunological and pharmacologic properties of the claimed antibody to enable one of skill in the art to treat HIV infection, or prevent AIDS onset, without undue experimentation.

In particular, the Examiner alleges that the instant disclosure fails to provide *any* guidance pertaining to the binding specificity, affinity, avidity, half-life, or circulating titer

required to achieve a therapeutic response. The Examiner also supports the rejection on the ground that the use of immunotherapy in the treatment or prevention of HIV infection is unpredictable, in view of alleged previous failures resulting from low binding affinity, rapid clearance rates, the quasispecies nature of HIV infection, and the ability of the virus to reside in immunoprivileged sites. However, no evidentiary basis is provided for such an assertion.

The Examiner also contends that the therapeutic effectiveness of the claimed antibody also relies upon its ability to induce apoptosis of HIV-infected cells, but that Applicants' working examples only demonstrate that the 2G9 antibody induces apoptosis in ~20% of the cell population examined. The Examiner, again without providing any evidentiary basis, contends that such would not have any "meaningful clinical effect."

Applicants disagree, and traverse the rejection, respectfully, in view of the following remarks.

Initially, Applicants note that Claim 10 is canceled herewith, without prejudice or disclaimer, mooting the rejection of this claim.

Regarding Claim 9, Applicants note that Claims 8 and 11 are not rejected under section 112, first paragraph, indicating that the Office acknowledges that the specification is enabling for at least one use reasonably correlating with the scope of these claims. In this regard, Applicants note that Claim 9 as amended merely claims a composition comprising the antibody of Claim 8 or 11, and a pharmaceutically acceptable carrier, and no longer recites an intended use of the composition to treat HIV infection, or prevent AIDS onset. Thus, the subject matter of Claim 9 is enabled at least for the same reasons as Claims 8 and 11 are enabled.

Nevertheless, and independent of the above, for the following reasons, Applicants respectfully submit that the specification *is* enabling for the treatment of HIV and AIDS, and

thus the subject matter of new Claim 12, a process-of-use claim directed to the treatment of HIV and AIDS using the antibody of Claim 8 or 11, is enabled.

First, regarding the Examiner's assertion that the instant disclosure fails to provide *any* guidance pertaining to the binding specificity, affinity, avidity, half-life, or circulating titer required to achieve a therapeutic response, Applicants respectfully disagree. Applicants respectfully refer the Examiner to the myriad of therapeutic antibodies known in the art to bind to, and cause cytolysis of, antigen-expressing cells (and which have been shown to be efficacious *in vitro* and *in vivo*, and are FDA-approved), such as Retuximab®, Tositumomab® and Ibritumomab® (for the treatment of non-Hodgkin's lymphoma), which bind CD20 on B-lymphocytes, Alemtuzumab® (for the treatment of B-cell chronic lymphocytic leukemia (B-CLL)), which binds to CD52 on mature lymphocytes, Mylotarg® (for the treatment of acute myeloid leukemia (AML), and Palivizumab® (for the treatment of RSV infections). At the time of the invention, the art was replete with the efficacious use of immunotherapy for a variety of conditions, and the considerations for using antibodies in a therapeutic setting, such as determining half-life, and circulating titer, were matters of routine skill in the art.

Second, regarding the Examiner's assertion that Applicants' working examples only demonstrate that the 2G9 antibody induces apoptosis in ~20% of HIV-infected cells, and that such would not result in any "meaningful clinical effect," Applicants respectfully point out that such represents a mischaracterization of the data in Applicants' disclosure. Applicants respectfully point out that Example 3 in the specification as filed, which appears to be the basis of the Examiner's assertion, pertains to the efficacy of the claimed antibody in apoptosing **latently-infected** cells. Whilst Applicants consider that such efficacy would be appreciated by one of skill in the art as having therapeutic significance, because one of skill in the art would

understand that current HIV treatments are limited to the inhibition of HIV virus *replication* (*i.e.*, they are unable to eliminate latently-infected cells containing integrated provirus, but which are not undergoing viral replication), Applicants nonetheless refer the Examiner to Figure 3, which depicts the data obtained in the experiments of Example 2. Figure 3 demonstrates that when the 2G9 antibody is contacted with infected cells undergoing viral replication, that is, *productively-infected cells*, **all** of the productively-infected cells were apoptosed. Such is made explicit on page 10 of the specification as filed, where Applicants state that "[a]s shown in Fig. 3, while the cells were not [TUNEL] stained when the cells were not treated with 2G9 antibody, the cells were **completely** [TUNEL] stained after cultivating in the presence of 2G9 antibody." (Emphasis added.) Thus, as experimentally demonstrated by Applicants, the 2G9 antibody was able to induce apoptosis in **all** cells productively infected with HIV, and also in more than 20% of the cells that were latently infected. One of skill in the art would readily appreciate that such an antibody may thus be used to treat HIV and AIDS, because those skilled in the art were aware that destruction of productively infected cells inhibits viral production, thus reducing viral load in a patient. At the time of the invention, the art recognized HIV viral load as strongly correlating with HIV progression to AIDS, and with a poor prognosis.

Although the Examiner takes the position that in the absence of predictive data between *in vitro* inhibition, and *in vivo* efficacy, one of skill in the art would be unable to predict the efficacy of the claimed antibody in the treatment of AIDS, Applicants respectfully disagree. The Examiner has provided no sound reasoning as to why one of skill in the art would be unable to predict that the claimed antibody would be useful in the treatment of HIV and AIDS. Pursuant to MPEP §2164.02, in finding a lack of enablement, "the examiner *must* also give reasons for a conclusion of lack of correlation for an *in vitro* or *in vivo* animal model example. A rigorous or

an invariable exact correlation is not required, as stated in *Cross v. Iizuka*, 753 F.2d 1040, 1050, 224 USPQ 739, 747 (Fed. Cir. 1985)." (Emphasis added.) At the time of the invention, the state of the art of immunotherapy was sufficiently mature such that one skilled in the art would understand that antibodies demonstrating the potency of the claimed antibody *in vitro*, that is, an antibody capable of inducing apoptosis in *all* productively-infected cells, would be predicted to demonstrate efficacy *in vivo*.

Further still, Applicants note that a finding of enablement in the instant case does not turn on whether the claimed antibody is able to *cure* HIV or AIDS, but rather, whether it may be used as a treatment. Applicants respectfully point out that all the anti-HIV drugs of clinical importance and efficacy remain unable to provide a curative effect, but rather, are used merely to improve quality of life and extend life expectancy. Similarly, Applicants do not claim a method for eradicating HIV, or curing AIDS, and a rejection for lack of enablement predicated on such is improper.

In view of the foregoing, Applicants respectfully submit that the specification is enabling for the claimed subject matter.

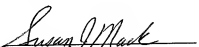
Withdrawal of the rejection is respectfully requested.

Conclusion

In view of the above, reconsideration and allowance of this application are now believed to be in order, and such actions are hereby solicited. If any points remain in issue which the Examiner feels may be best resolved through a personal or telephone interview, the Examiner is kindly requested to contact the undersigned at the telephone number listed below.

The USPTO is directed and authorized to charge all required fees, except for the Issue Fee and the Publication Fee, to Deposit Account No. 19-4880. Please also credit any overpayments to said Deposit Account.

Respectfully submitted,



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